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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/813,760	03/31/2004	Joel E. Bernstein	41959-102739	5267

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EXAMINER	
KWON, BRIAN YONG S	

ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
08/06/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Patent-ch@btlaw.com

Office Action Summary	Application No.	Applicant(s)	
	10/813,760	BERNSTEIN, JOEL E.	
	Examiner	Art Unit	
	Brian-Yong S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3, 5-9 and 11-37* is/are pending in the application.

4a) Of the above claim(s) *16-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-9 and 11-15* is/are rejected.

7)☐ Claim(s) _ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/22/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. Acknowledgement is made of applicant's Amendment/Remarks filed on 04/09/2009. By the amendment, claims 1, 3, 9, 11 and 13 have been amended. Claims 1-3, 5-9 and 11-15 are currently pending for prosecution on the merits.

2. It is noted that applicant has received an action on the merits for the originally elected invention which is directed to a Group I Invention along with acetaminophen as the elected species (see page 4, line 5 of the O.A. mailed 11/29/2006; page 5, line I of Applicant's Remarks filed 02/28/2007). Since claims 1-3, 5-9 and 11-15 are not ready for allowance, applicant is not entitled to consideration of claims to additional species recited in claims 16-17. Accordingly, the examiner determines that it is proper to withdraw claims 16-17 from further consideration as being drawn to non-elected invention.

3. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of actions being applied to the instant application.

Information Disclosure Statement

4. Enclosed is an initialed copy of PTO 1449 filed 06/22/2009 which has been considered for your records.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1-3, 5-9 and 11-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kroger et al. (Gen. Pharmac., Vol. 28, No. 2, pp. 257-263, 1997), and further in view of Ogata et al. (USP 5478815) and Murdock (USP 4526788).

Kroger teaches use of combination of nicotinamide (12.5mg/kg IP or from 25 mg/kg to 100mg/kg IP) and methionine (12.5mg/kg IP or from 25 mg/kg to 100mg/kg IP) in decreasing hepatotoxicity induced by the hepatotoxic compound such as 500mg/kg of acetaminophen (abstract; Figure 2; Results; Discussion). Kroger teaches that the combination of l-methionine and nicotinamide even at lower dose of 12.5mg/kg IP each synergistically results in complete protection from acetaminophen-induced release of GOT and GPT.

Ogata is being provided as a supplemental reference to demonstrate the routine knowledge (in pharmaceutical art) in using intraperitoneal injection as experimental animal testing for the administration of systemic or oral drugs (Examples; column 2, lines 28-31).

Murdock is being provided as a supplemental reference to demonstrate the routine knowledge (in pharmaceutical art) in calculating human dosage based on the interrelationship of dosages for animals of various sizes and species and humans described by Freireich, E. J., et. al., Rep., 50, No. 4, 219-244, May 1966 (column 5, lines 45-51).

Kroger differs from the claimed invention in (i) the preparation of a composition comprising acetaminophen, nicotinamide and methionine in the specific amounts, namely about 80-1000 mg dose of acetaminophen, about 5 mg to about 500 mg dose of methionine and about 10 mg to about 500 mg dose of nicotinamide, per standard dose, (ii) the preparation of said composition in various dosage forms, namely oral or sterile solutions or suspensions form, more preferably tablets, capsules, caplets, intradermal, subcutaneous, intramuscular, intravenous or intrathecal.

One having ordinary skill in the art would have expected as taught by Kroger that the combination of methionine and nicotinamide would provide protection from acetaminophen-

induced liver damage and motivated to make such modification to prepare known hepatotoxic drug such as acetaminophen with nicotinamide and methionine combination in various pharmaceutical dosage forms to accommodate patient's preference and needs where the compliance could be improved with effective and well tolerated dosage form. One having ordinary skill in the art would have expected at the time of the invention was made that the results from Kroger could apply to the development of other modes of administration, for example systemic and/or oral administration. As discussed in preceding comments, it was known at the time of the invention was made that intraperitoneal injection is used as experimental animal testing for the administration of systemic or oral drugs (due to ease of administration compared with other parenteral methods in animal study). Thus, one having ordinary skill in the art has basis for perceiving Kroger's study as constituting recognized animal study with clear relevance to utility systemic and/or oral administration in humans.

One would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

Determination of the specific dosage amounts of each ingredient in said composition and/or the specific delivery dosage forms, those of ordinary skill in the art would have been readily optimized effective dosages amounts and/or dosage forms as determined by good medical practice and the clinical condition of the individual patient. Regardless of the manner of administration, the specific dose would have been calculated according to body weight, body surface area or organ size. Determination of the appropriate dosage amounts or dosage forms for

treatment involving each of the above mentioned formulations would have been routinely made by those of ordinary skill in the art and is within the ability of tasks routinely performed by them without undue experimentation, especially in light of the dosage information disclosed in the above prior art references. For example, the referenced 12.5 mg/kg dose of methionine or nicotinamide in mouse is equivalent to 1.04 mg/kg in human (base on Freireich EJ. Et al., 1966 conversion factor) which falls within the instantly claimed dosage range of either methionine or nicotinmaide. Therefore, the references in combination make obvious the instant invention.

Generally, differences in dosage amounts or dosage forms will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such dosage amounts or dosage forms is critical. Where the general conditions of a claim are disclosed in the prior art, it not inventive to discover the optimum or workable dosage amounts or dosage forms by routine experimentation.

Response to Arguments

6. Applicant's arguments and Exhibits filed 04/09/2009 have been fully considered but they are not persuasive.

Applicant's argument in the response takes the position that there are three elements of the pending claims which are not taught by Kroger. Applicant sates:

a Route of administration – In Kroger, nicotinamide or methionine or their combination are administered intraperitoneally ("IP"). This is a very substantive

difference from the routes of administration claimed in the present application. First, IP is virtually never used in humans[1-2] for two principal reasons: (a) IP provides significantly faster and more substantial blood levels of drugs[1-3] than other routes of administration; and (b) risk of infection and bowel adhesions are unwarranted for use of this route in humans[1]. There are no drugs approved for IP administration to humans in North America or Europe.

b. Composition and Method – In Kroger, nicotinamide and/or methionine are administered as separate IP injections, and the acetaminophen and methotrexate are administered orally or by IP respectively at an earlier time point. In contrast, in the compositions cited in the pending application, all components (the hepatotoxic active drug agent and the hepatoprotective agents - nicotinamide, methionine, and folic acid) are provided in the same dosage form and administered together in this dosage form (e.g. capsule, tablet, solution).

c. The dosages of nicotinamide and methionine administered IP for protective effects by Kroger are very substantially greater than those administered orally or by injection (but not IP), in the present application. IP dosages used by Kroger range from 25-100 mg/kg nicotinamide and 50-300 mg/kg methionine when each is given alone, to 12.5 mg/kg of each when they are both administered in separate IP injections. Based on the average body weight for adult Americans[4] the dosage of nicotinamide in the claims of the present application ranges from .11 mg/kg to 5.7 mg/kg for males and from .13 mg/kg to 6.7 mg/kg for females, and the dosage of methionine in claims of the present application ranges from .29 mg/kg to 5.7

This argument is not found persuasive. Unlike the applicant's argument, there are preponderous of evidences indicating that intraperitoneal injection (IP) is routinely used in animal testing for the administration of systemic drugs and fluids due to the ease of administration compared with other parenteral or oral methods. For instance, US 4314989 discloses an experimental animal testing for the separate IP administration of acetaminophen and methionine sulfoxide acetaminophen (column 3, line 60 through 26). US'989 contemplates and/or concludes that (non-toxic effective amount of) methionine sulfoxide reduces the hepatotoxic effects of acetaminophen and claims for a pharmaceutical composition comprising acetaminophen in admixture with a non-toxic amount of methionine sulfoxide, which intended

for human use (claims 8-10). Similarly, US 2009/0124606 discloses an experimental animal testing for the IP administration of haloperidol where deramciclane is administered orally (Examples). US'606 contemplates and/or concludes that deramciclane is effective in decreasing or eliminating the extrapyramidal side effects caused by antipsychotic drugs such as haloperidol and claims for a pharmaceutical composition comprising deramciclane and haloperidol, broadly an antipxychotic agent in combination with deramciclane, which is intended for human use (claims 1-16).

As discussed in preceding comments, an experimental animal study using IP administration or IP administration in combination with other modes of administration (e.g., IV and oral) is routinely utilized to study the efficacy of particular drugs (see also "Experimental Method" and claims in US 5284861; column 8, lines 5 through column 10, line 13 and column 6, line 65 through column 7, line 10 in US 7557142 for your references). Thus, one having ordinary skill in the art would have expected as taught by Kroger coupled with the state of art knowledge that methionine and nicotinamide combination would provide protection from acetaminophen-induced liver damage and motivated to make such modification to prepare known hepatotoxic drug such as acetaminophen in mixture with nicotinamide and methionine combination in a pharmaceutically acceptable carrier, including various pharmaceutical dosage forms. One having ordinary skill in the art has basis for perceiving Kroger's study as constituting recognized animal study with clear relevance to utility systemic and/or oral administration in humans.

Again, with respect to the determination of suitable dosage forms, there are general references (see USP 6733797 B1; USP 6048846; USP 4581348; USP 4401657; USP 4837239; Kegon'kova et al., Eksp. Klin Farmakol., 1997, abstract, 1997, 60(2):68-71) indicating that

pharmaceuticals containing nicotinamide and methionine alone or in combination generally may be delivered orals, as well as disclosing benefits to be achieved by orals versus other modes of administration (i.e., parenteral). Therefore, there exist general art accepted motivations for formulating drugs for oral administration. Furthermore, determination of appropriate dosage amounts for treatment of intended purpose involving each of the above mentioned formulation is routinely made by those of ordinary skill in the art and is within the ability of tasks routinely performed by them without undue experimentation, especially in light of the prior art (see also USP 6733797; USP 4581348; USP 6048846). Thus, the examiner maintains the rejection of the record.

In response to applicant's argument that "the dosages of nicotinamide and methionine administered IP for protective effects by Kroger are very substantially greater then those administered orally or by injection…", the examiner recognizes that determination of the specific dosage amounts of each ingredient in said composition and/or the specific delivery dosage forms, those of ordinary skill in the art would have been readily optimized effective dosages amounts and/or dosage forms as determined by good medical practice and the clinical condition of the individual patient. Regardless of the manner of administration, the specific dose would have been calculated according to body weight, body surface area or organ size. Determination of the appropriate dosage amounts or dosage forms for treatment involving each of the above mentioned formulations would have been routinely made by those of ordinary skill in the art and is within the ability of tasks routinely performed by them without undue experimentation, especially in light of the dosage information disclosed in the prior art references (see also column 3, lines 5-29 of US 5994410 and column 203, lines 23-54 of US 6881401 for your addition

references). For example, the referenced 12.5 mg/kg, 25mg/kg and 50 mg/kg doses of methionine or nicotinamide in mouse is equivalent to 1.04 mg/kg, 2.08 mg/kg and 4.16 mg/kg in human, respectively (based on Freireich EJ. Et al., 1966 conversion factor, see attached PTO 892 form) which falls within the instantly claimed dosage range of either methionine or nicotinmaide. Therefore, the examiner maintains that the references in combination make obvious the instant invention.

In response to the applicant's argument that the unpredictability of animal testing reported in Exhibits D, E & F indicates that results of clinical studies that are the basis fro present claims, are not obvious over animal studies", the examiner recognizes the contrary to the applicant's argument, there are numerous evidences showing in the state of art (US 4314989, US 7557142, US 5284861, US 5059592, US 5804567, US 6465511, US 3983250, etc…) that data from animal model study is generally sufficient to support therapeutic utility or pharmacological utility for a compound, composition or process. The examiner determines that one having ordinary skill in the art has basis for perceiving Kroger's study as constituting recognized animal study with clear relevance to utility systemic and/or oral administration in humans or animals.

In response to applicant's argument that Exhibit H shows IP is not employed for treatment of human, this argument is basically the same as discussed above, so the response discussed above applies here as well and is unpersuasive for reason just discussed

Conclusion

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. No Claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

/Brian-Yong S Kwon/

Primary Examiner, Art Unit 1614